Richard Southern, famous Balliol historian and medievalist, was very taken with a 13th century German theologian and philosopher called Meister Eckhart. Eckhart, persecuted by the Inquisition, generally seems to have been a good bloke, as well as having a good line in quotes. One Bandolier likes is "*Truth is something so noble that if God could turn aside from it, I could keep the truth and let God go*". The trouble is that rules of truth as they apply in our field are forever overlooked, or over-ridden by other considerations. There are inevitable limitations, and we almost always see some part of a particular truth through a glass, darkly.

In this last paper issue, Bandolier looks at issues and topics where the truth is hard to out. First a moan on known limitations of evidence that are so often ignored. Then a few examples: first of surfactant in paediatric intensive care use, with lots of sharp spicules to puncture pre-formed opinions or unconsidered simplifications. Then there are the eternal questions – does coenzyme Q10 have any value except to empty your pockets?

Internet Bandolier

"*Only those who have dared to let go can dare to reenter*". Another Eckhartism. Internet Bandolier will still be there, but is going to change. Various ideas are being considered, and will be implemented as soon as time permits.

And finally

Thanks for reading Bandolier for 161 issues and 14.5 years. Eckhart has the words "*If the only prayer you said in your whole life was, "Thank You", that would suffice*".

And finally, finally

Q: When was the world's first international sports match?
A: In 1840/1850s, cricket matches between the USA and Canada.

Doesn't a little knowledge change your view of the world?

In this issue

ON LIMITATIONS

The thing about looking at evidence of any sort is that there are likely to be limitations to it. Trials may not be properly conducted, measure outcomes that are not useful, be conducted on patients not like ours, or present results in ways that we can easily comprehend; trials may have few events, when not much happens, but make much of not much, as it were. Observational studies, diagnostic studies, and health economic studies all have their own particular set of limitations, as well the more pervasive sins of significance chasing, or finding evidence to support only preconceptions or *idées fixes*.

Perfection in terms of the overall quality and extent of evidence is never going to happen, if only because the ultimate question - whether *this* intervention will work in *this* patient and produce *no* adverse effects – cannot be answered. The average results we obtain from trials are difficult to extrapolate to individuals, and especially the patients in front of us.

Acknowledging limitations

Increasingly we have come to expect authors to make some comment about the limitations of their studies, even if it is a nod in the direction of acknowledging that there are some. This is not easy, because there is an element of subjectivity about this. Authors may also believe, with some reason, that spending too much time rubbishing their own results will result in rejection by journals, and rejection is not appreciated by pointy-heads.

Even so, the dearth of space given over to limitations of studies is worrying. A recent survey [1] that examined 400 papers from 2005 in the six most cited research journals and two open-access journals showed that only 17% used at least one word denoting limitations in the context of the scientific work presented. Among the 25 most cited journals, only one (JAMA) asks for a comments section on study limitations, and most were silent.

Few events

It is an unspoken rule that, to have a paper published, it helps to have some measure that displays a statistically significant difference. This leads to the phenomenon of significance chasing, in which data are analysed to death, and the aim is any test that shows significance at the paltry level of 5%. One issue arising is correcting for multiple statistical testing, something almost never done, as pointed out in Bandolier 153.

The more important question, not asked anything like often enough, is whether any statistical testing is appropriate. Put another way, when can we be sure that we have enough information to be sure of the result, using the mathematical perspective of sure, meaning the probability to a certain degree that we are not being mucked about by the random play of chance? This is not a trivial question, given that many results, especially concerning rare but serious harm, are driven by very few events.

A few older papers keep being forgotten. When looking at the strengths and weaknesses of smaller meta-analyses versus larger randomised trials, a group from McMaster [2] suggested that with fewer than 200 outcome events research (meta-analyses in this case) may only be useful for summarising information and generating hypotheses for future research.

A different approach using simulations of clinical trials and meta-analyses [3] arrived at pretty much the same conclusion, that with fewer than 200 events the magnitude and direction of an effect becomes increasingly uncertain.

Just how many events is needed to be reasonably sure of a result when event rates are low (as in the case for rare but serious adverse events) was explored some while ago [4]. Bandolier's best try at explaining lots of maths and tables appears in Table 1. This looks at a number of examples, varying event rates in experimental and control groups, using probability limits of 5% and a more stringent one of 1%, and with the power of 80% and 90% to detect an effect.

Higher power, greater stringency in probability values, lower event rates, and smaller differences in event rates between groups all militate towards needing more events

and larger numbers of patients in trials. Once event rates fall to about 1% or so, and differences between experimental and control to less than 1%, the number of events needed approaches 100 and number of patients rises to tens of thousands.

Subgroup analyses

One of the best examples of the dangers of subgroup analysis, due to unknown confounding, comes from a review article [5]. It examined the 30-day outcome of death or myocardial infarction from a meta-analysis of platelet glycoprotein inhibitors. Analysis indicated different results for women and men (Figure 1), with benefits in men but not women. Statistically this was highly significant ($p<0.0001$).

In fact, it was found that men had higher levels of troponins (a marker of myocardial damage) than women, and when this was taken into account the difference between men and women is understandable, with more effect with greater myocardial damage; sex wasn't the source of the difference.

Figure 1: Subgroup analysis in women and men of death or MI with platelet glycoprotein inhibitors (95% confidence interval)
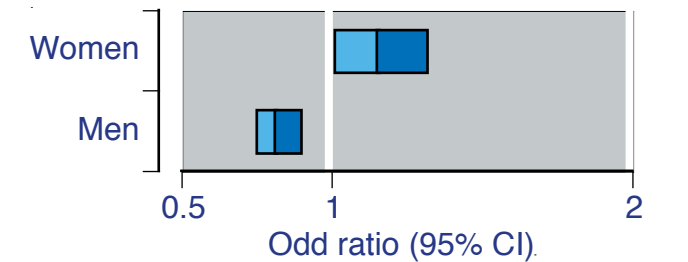
Table 1: Examples of numbers of events and numbers of subjects required to be reasonably sure of the direction of a result at various levels of significance and power for rare events

Event rates (probabilities)		Mean event rate (%)	Power of 80%				Power of 90%			
			p<0.05		p<0.01		p<0.05		p<0.01	
Experimental	Control		Events	Total	Events	Total	Events	Total	Events	Total
0.1	0.01	5.5	12	218	14	255	15	273	21	382
0.01	0.001	0.55	12	2182	14	2546	15	2727	21	3818
0.001	0.0001	0.055	12	21818	14	25455	15	27273	21	38182
0.1	0.05	7.5	67	893	>75	>1000	>75	>1000	>75	>1000
0.01	0.005	0.75	67	8933	>75	>10000	>75	>10000	>75	>10000
0.001	0.0005	0.075	67	89333	>75	>100000	>75	>100000	>75	>100000
0.04	0.01	2.5	23	920	34	1360	29	1160	42	1680
0.004	0.001	0.25	23	9200	34	13600	29	11600	42	16800
0.0004	0.0001	0.025	23	92000	34	136000	29	116000	42	168000
0.03	0.01	2.0	33	1650	48	2400	42	2100	59	2950
0.003	0.001	0.2	33	16500	48	24000	42	21000	59	29500
0.0003	0.0001	0.02	33	165000	48	240000	42	210000	59	295000
0.02	0.01	1.5	>75	>5000	>75	>5000	>75	>5000	>75	>5000
0.002	0.001	0.15	>75	>50000	>75	>50000	>75	>50000	>75	>50000
0.0002	0.0001	0.015	>75	>500000	>75	>500000	>75	>500000	>75	>500000

Table 2: What different levels of relative risk actually mean

Relative risk	What this means
<1.0	The risk of an event is reduced for the experimental intervention compared with the control intervention
1.0	No increased or decreased risk for experimental versus control
1.0 - 2.0	Higher risk of events with experimental intervention, but most events occur because of underlying factors - like the patient population being studied
>2.0	Higher risk of events with experimental intervention, and most events occur because of the experimental intervention

Trivial differences

It is worth remembering what relative risks tell us in terms of raw data (Table 2). Suppose we have a population in which 100 events occur with our control intervention, whatever that is. If we have 150 events with an experimental, the relative risk is now 1.5. It may be statistically significant, but most events were those occurring anyway. If there were 250 events, the relative risk would be 2.5, and now most events would occur because of the experimental intervention.

Large relative risks may be important, even with more limited data. Small relative risks, probably below 2.0, and certainly below about 1.5 should be treated with caution, especially where the number of events is small, and even more especially outside the context of the randomised trial.

The importance of a relative risk of 2.0 has been accepted in US courts [6]. "*A relative risk of 2.0 would permit an inference than an individual plaintiff's disease was more likely than not caused by the implicated agent. A substantial number of courts in a variety of toxic substance cases have accepted this reasoning.*"

Confounding by indication etc

Bias arises in observational studies when patients with the worst prognosis are allocated preferentially to a particular treatment. These patients are likely to be systematically different from those not treated, or treated with something else (paracetamol, rather than NSAID in asthma, for instance).

Confounding, by factors known or unknown, is potentially a big problem, because we do not know what we do not know, and the unknown could have big effects – like troponin above. When relative risks are small, say below about 1.3, potential bias created because of unknown confounding, or confounding by indication improperly adjusted, becomes so great that it makes any conclusion at best unreliable.

Comment - the uncertainty principle

These are just a few of the limitations Bandolier sees in papers and talks. There are more, obviously. Worst of all is an outcome failing to reach statistical significance at a trivial level like 5% despite multiple statistical comparisons then being trumpeted as a "result", and extrapolated to whole populations. If it ain't statistically significant, it don't signify.

The trouble is that we live in an imperfect world, where we never have the truth, the whole truth, and nothing but the truth on which to work and build judgements. We have to make do with what we have, and try our best to exclude the rubbish. Some try a philosophical approach to calculate thresholds above which we can begin to believe [7], but that seems a bit too glib.

References:

1   JPA Ioannidis. Limitations are not properly acknowledged in the scientific literature. Journal of Clinical Epidemiology 2007 60: 324-329.
2   MD Flather et al. Strengths and limitations of meta-analysis: larger studies may be more reliable. Controlled Clinical Trials 1997 18: 568-579.
3   RA Moore et al. Size is everything - large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1998 78: 209-16.
4   JJ Shuster. Fixing the number of events in large comparative trials with low event rates: a binomial approach. Controlled Clinical Trials 1993 14: 198-208.
5   SG Thompson, JPT Higgins. Can meta-analysis help target interventions at individuals most likely to benefit? Lancet 2005 365: 341-346.
6   Annual Reference Manual on Scientific Evidence 2nd Edition, 2005-2006, p539 (ISBN 0820547549).
7   B Djulbegovic, I Hozo. When should potentially false results be considered acceptable? PLoS Medicine 2007 4:2:e26.

SURFACTANT FOR ACUTE RESPIRATORY FAILURE IN CHILDREN

The use of exogenous pulmonary surfactant in the respiratory distress syndrome of the newborn is known to reduce mortality by almost half, as well as having other benefits. The use of surfactant in that setting is well understood, and forms part of several guidelines.

The benefits of using pulmonary surfactant in other settings is less clear, and the specific example of its use in acute respiratory failure in children [1] makes for interesting reading, with some lessons for decision-makers.

Systematic review

The review searched several databases (to about 2005), together with bibliographies, trial registries, and conference proceedings. Randomised trials were included comparing pulmonary surfactant plus standard care with standard care alone in intubated, mechanically ventilated patients with acute respiratory failure. Studies in neonates with respiratory distress syndrome were not part of the review. At least one dose of surfactant had to be used.

Table 1: Main outcomes of clinical trials of surfactant in paediatric patients with respiratory failure

	Group B <1 year RSV	Group B 4-7 years ARDS
Number	79	226
Mean death rate (%)	0	28
Absolute difference surfactant - control		
Mortality (%)	0	-13
Ventilator free days to day 28	2.2	1.9
Days of mechanical ventilation	-2.2	-1.1
Days of paediatric intensive care	-2.9	0.3

Outcomes sought were all case mortality, number of ventilator-free days to day 28, duration of mechanical ventilation, duration of stay on paediatric intensive care unit, and others, like adverse events.

Results

Six studies (311 patients) were found, two with blind intensive care teams. Three trials enrolled 79 infants aged mostly below one year with respiratory syncytial virus induced respiratory failure or severe bronchiolitis; there were no deaths in this group which we will call group A. Three other trials enrolled 226 children of average age four to seven years with acute respiratory distress syndrome or acute lung injury, including pneumonia, sepsis, and near drowning; in this group the mortality rate averaged 28% (group B).

The main results are shown in Table 1. For group A, there were more ventilator free days, fewer days of mechanical ventilation, and fewer days on the paediatric intensive care unit on average. For group B, older children, there were more ventilator free days and fewer days of mechanical ventilation. In addition, there was a 13% reduction in mortality (NNT to prevent one death 8 (95% confidence interval 4 to 220)). There were no adverse events directly related to the use of surfactant.

Comment

Surfactant is not inexpensive, running at several hundreds of pounds per dose, and most of these trials used one or two doses, though one could use up to four. Cost could be an issue in deciding whether or not pulmonary surfactant should be used.

So what does the evidence tell us? The first step might be to ask whether there are any further trials that can help us, and, indeed, one more [2] adds a further 42 children. The full story on mortality for trials with any deaths is shown in Figure 1. A brief glance, or more analysis, shows that the higher the baseline risk of death, the more use of surfactant is likely to prevent a death; in the two trials with death rates above 15%, the NNT to prevent a death was 6.

Figure 1: Mortality with surfactant and control in trials with any deaths
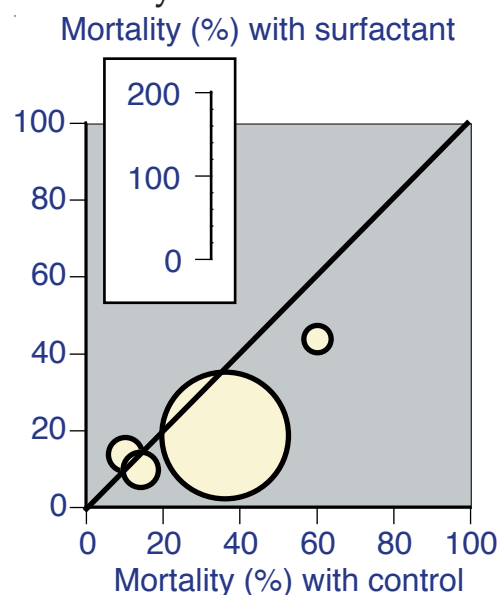
On other measures use of surfactant also produced benefits. In particular, a reduction of almost three days in paediatric intensive care for group A speaks to substantially lower costs, even where mortality was not an issue. In group B, these other benefits are not obvious, but the largest trial in group B did measure overall hospital costs, which were US$1,200 less per patient with surfactant. A cost-effectiveness analysis [2] agrees that costs were lower with surfactant.

The case looks pretty solid, though it is easily possible to take a "glass half empty approach". For instance, the statistical significance achieved for mortality was bare, with an upper confidence interval just below 1. A change of one or two deaths would remove statistical significance. Moreover, the two trials with the largest benefits on other outcomes have impossibly small standard deviations, and because of the way results are weighted by variance, these two trials carry 50% of the weight with only 20% of the patients. That doesn't make sense, but may influence our views. The results in Table 1 have used a more conservative approach, using weighting by trial size; the trouble is, though, that probably none of these results are now statistically significant.

All of which makes this [1] a most interesting paper and subject for discussion; it would certainly be a useful teaching paper. What's the bottom line? It may be that surfactant should be used despite no rigorous evidence of benefit, because it helps oxygenation, or for other technical reasons. It is a decision that requires a bit of wisdom, and shows the limitations of evidence without a bit of thought and wisdom.

References:

1 M Duffett et al. Surfactant therapy for acute respiratory failure in children: a systematic review and meta-analysis. Critical Care 2007 11: R66 (doi:10.1186/cc5944).
2 NJ Thomas et al. Cost-effectiveness of exogenous surfactant therapy in pediatric patients with acute hypoxic respiratory failure. Pediatric Critical Care Medicine 2005 6: 160-165.

COENZYME Q10 AND MIGRAINE

Coenzyme Q10 has been like an old but embarrassing friend to Bandolier. Over the years, many readers have asked for an appreciation of the evidence relating to all the wonderful health-giving properties it supposedly has. Ever obedient, Bandolier scurries off to look for this evidence, but finds none – hence the embarrassment.

It is ironic, then, that just now there is a smidgin of evidence that Q10 may be useful in preventing frequent headaches and/or migraine. The dictionary definition of smidgin is a tiny or scarcely detectable amount, so don't hold your breath for anything exceptional.

Search

Searching was fairly simple, looking for articles with coenzyme Q10, ubiquinone, and/or headache or migraine. Any study was accepted, cohort or randomised trial, as long as it reported some indicator of frequency of migraine or headaches, principally as the number of patients with at least a 50% reduction in the number of migraine or headache attacks (number per month) or days affected per month.

Results

Three studies were found, two cohorts, and one randomised trial, all published since 2002.

Cohort studies

The first cohort [1] included 32 patients with International Headache Society-defined migraine for at least one year, and usually with two to eight migraine attacks each month. All were seen by a neurologist before study entry, and a full history and examination performed. Treatment consisted of a baseline month followed by three months of coenzyme Q10 at 150 mg daily, given once in the morning.

Among the 31 completers, 19 (61%) had at least 50% reduction in headache days per month, and 29 (93%) had at least a 25% reduction (average of last two months on treatment). The mean number of days per month with headache fell from 7.3 to 3.0. The mean number of attacks fell from 4.9 per month at baseline to 2.8 during the last two months of treatment. There was no difference in severity of headache or associated symptoms, and no adverse events reported with coenzyme Q10.

The second cohort [2] reported on a consecutive series of 1,550 paediatric and adolescent patients with migraine (ICD classification) in whom a series of coenzyme Q10 measurements were made. The reference range used for serum coenzyme Q10 was 0.5 to 1.5 mg/L; 1143 had levels below 0.7 mg/L and 510 had levels below 0.5 mg/L. Coenzyme Q10 supplementation was recommended (at 1 to 3 mg/kg/day) for those below 0.7 mg/L.

In 252 young patients who took supplements and who had follow up data, mean serum coenzyme Q10 levels rose from 0.5 to 1.2 mg/L, with a large increase in those with levels

Figure 1: At least 50% reduction in headache frequency (dark) or days (light)
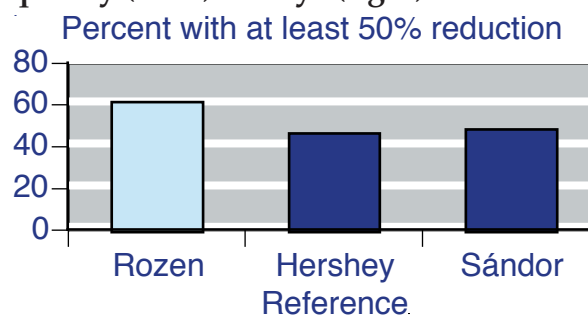
initially below 0.7 mg/L. In those taking supplements, there was at least a 50% reduction in headache frequency in 46%. The average number of headache days per month fell from 19 to 13.

Randomised trial

This trial [3] randomised 43 patients with IHS-defined migraine occurring two to eight times a month to 300 mg coenzyme Q10 daily or placebo. The trial was of good quality (properly randomised and double blind), but six patients dropped out after randomisation. A baseline month was followed by three months of treatment.

The proportion of patients with at least a 50% reduction in attack frequency was 3/21 (14%) with placebo and 10/21 (48%) with coenzyme Q10 for the last month of treatment compared with baseline. There was no difference in migraine severity, but there were fewer migraine days and days with nausea or vomiting.

Comment

As Figure 1 shows, there was a consistent improvement for major reduction in headache frequency or days of headache per month in both cohort studies and the randomised trial. Half the people involved had a major benefit in headache reduction.

But the evidence itself is not extensive. The total number of patients on coenzyme Q10 was about 300, and with only a single small randomised trial of good quality there is not sufficient good evidence to be sure of benefit (or adverse events, come to that).

Let's face it, if a huge trial told us there was no effect, then we might not be surprised. But no such trial is likely. While coenzyme Q10 is being tested in a number of indications, no further trials in migraine prevention appear to have been registered, so this is all we have to go on right now.

References:

1   TD Rozen et al. Open label trial of coenzyme Q10 as a migraine preventive. Cephalalgia 2002 22: 137-141.
2   AD Hershey et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache 2007 47: 73-80.
3   PS Sándor et al. Efficacy of coenzyme Q10 in migraine prophylaxis: a randomized controlled trial. Neurology 2005 64: 713-715.

Coenzyme Q10 and
Statin myopathy

For some time there has been a view that the muscle pains associated with statins may be reversed by taking coenzyme Q10. The argument is that statins inhibit the biosynthesis of both cholesterol and ubiquinone (fancy name for coenzyme Q10), with resultant lowering of cholesterol and ubiquinone in blood, ubiquinone in muscle, and, as ubiquinone is involved in electron transport and ATP formation, fatigue and muscle pain.

Whether taking coenzyme Q10 helps overcome that muscle pain is another matter, but there are a few straws in the wind.

Systematic review

A systematic review [1] sought all the evidence linking coenzyme Q10 with statin-associated myopathy, searching for English language articles in a PubMed search to August 2006, together with examination of reference lists. While it examines animal and human studies, only the human studies are mentioned here.

Results

Circulating coenzyme Q10

The review found nine randomised trials and nine observational studies looking at effects of statins on circulating levels of coenzyme Q10. Most of these were of a few weeks duration, and involved fewer than 50 patients. The two studies with at least 100 patients, both randomised, observed reductions in circulating coenzyme Q10 of 22% and 27-38% in 120 and 1,049 people respectively at 12 weeks and one year.

Most of the reduction in circulating coenzyme Q10 is related to lower levels of LDL-cholesterol, and some studies suggest that absolute changes are less relevant than the coenzyme Q10/cholesterol ratio [2].

Muscle coenzyme Q10

Five studies looked at muscle levels, one finding and increase, one a decrease, and three no difference.

Mitochondrial function

There is no consistent message of impairment to muscle metabolism with statins, or any suggestion that coenzyme Q10 is related to any changes.

Clinical studies

There is a dearth of clinical studies of coenzyme Q10 supplementation in statin-associated myopathy. None was published in full at the time of the systematic review. Two subsequent reports of randomised trials are too small to be conclusive.

One [3] compared daily coenzyme Q10 100 mg with vitamin E at 400 IU daily in 32 patients with myopathic symptoms on statins. After 30 days overall pain severity decreased, and pain interfered less with activities of daily living, but most patients taking coenzyme Q10 still had some pain.

A second report [4] records a randomised trial that managed to recruit only three patients with statin-associated myopathy in 1.5 years, because patients stopped the statin, or were already taking coenzyme Q10. All three had low initial circulating coenzyme Q10 levels, and two had significant improvements in mobility and energy levels together with increased circulating levels on blind or open challenge.

Comment

There really is not much evidence that coenzyme Q10 is effective in combating fatigue and muscle pain with statins. For some patients it does make a difference, though. A number of randomised trials are ongoing, so perhaps this is a space worth watching. At least one more moderate sized trial is ongoing, completing by the end of 2007.

References:

1   L Marcoff, PD Thompson. The role of coenzyme Q10 in statin-associated myopathy. Journal of the American College of Cardiology 2007 49: 2231-2237.
2   AD Hershey et al. Coenzyme Q10 deficiency and response to supplementation in pediatric and adolescent migraine. Headache 2007 47: 73-80.
3   G Caso et al. Effect of coenzyme Q10 on myopathic symptoms in patients treated with statins. American Journal of Cardiology 2007 99: 1409-1412.
4   MM Reidenberg. Statins, lack of energy and ubiquinone. British Journal of Clinical Pharmacology 2005 59: 606-607.

Coenzyme Q10 in hypertension

Coenzyme Q10 is one of those universal food supplements that is recommended for just about every ailment, without much, if anything, in the way of evidence. For hypertension, though, there is a small amount of evidence, and a systematic review [1] pulls the results together.

Systematic review

The review used a number of databases to find studies published up to 2005 that described therapy of hypertension with coenzyme Q10. The main outcome was the change in systolic and diastolic blood pressure between start and end of the trial.

Results

Twelve studies were found. Three randomised trials (130 patients) compared 100 or 120 mg coenzyme Q10 daily with placebo for eight or 12 weeks. Mean systolic blood pressure was about 166 mmHg and diastolic about 92 mmHg, either with or without other antihypertensive treatments.

Figure 1: Reduction in systolic blood pressure with coenzyme Q10 and placebo in randomised trials
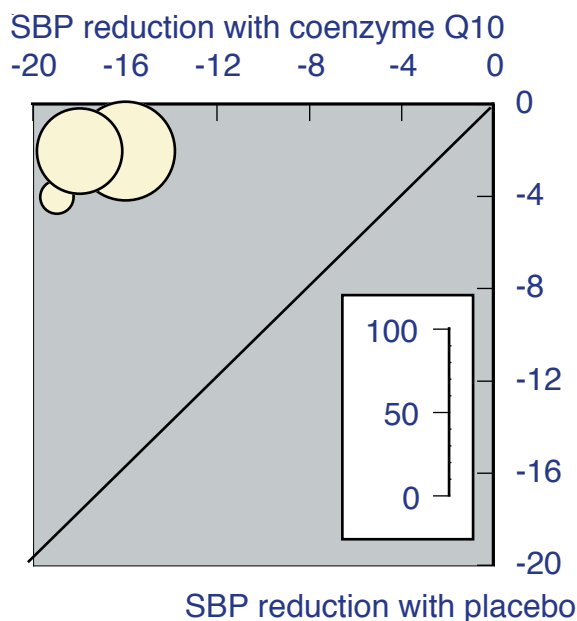
Coenzyme Q10 resulted in mean decreases in systolic blood pressure of about 15 mmHg more than placebo (Figure 1), and of about 3-7 mmHg more than placebo in diastolic blood pressure.

Eight open observational studies reported on four to 109 patients (214 total) taking 30 mg to 225 mg coenzyme Q10 daily for 1 to 56 weeks. The weighted mean decrease in systolic blood pressure was 13 mmHg (range 10-21 mmHg), and in diastolic blood pressure of 9 mmHg (range 6-16 mmHg).

Comment

The consistency between these studies gives a certain weight to these results, despite the small numbers. Moreover, another randomised trial in 74 patients with type 2 diabetes [2] compared 200 mg coenzyme Q10 daily with placebo over 12 weeks. It also achieved significant reductions in both systolic blood pressure by 6 mmHg more than placebo, and in diastolic blood pressure by 3 mmHg more than placebo.

Interestingly, HbA1c levels fell by about 0.4% more with coenzyme Q10 than with placebo, from initial moderate levels of about 7%.

Not a huge amount of information to go on, but better than a poke in the eye with a sharp stick. Right now there seem to be no new trials in this area, so that's all there is to go on to make any decisions on this topic.

References:

1   FL Rosenfeld et al. Coenzyme Q10 in the treatment of hypertension: a meta-analysis of the clinical trials. Journal of Human Hypertension 2007 21: 297-306.
2   JM Hodgson et al. Coenzyme Q10 improves blood pressure and glycaemic control: a controlled trial in subjects with type 2 diabetes. European Journal of Clinical Nutrition 2002 56: 1137-1142.

GOUT AND DRINKING

People with gout, and their carers, tend to the obsessive when it comes to food, and especially drinking; alcohol and coffee are often banned completely. All of which makes for a bland existence, which is why a frequently asked question is what gout sufferers can drink without exacerbating their condition. A large US survey has reported on coffee, tea, and various forms of alcohol [1,2]. The results will warm the cockles of some hearts.

Studies

A representative sample of the US population was selected and studied between 1988 and 1994. Subjects were interviewed at home, and attended an examination, with blood and urine sample collection. During the interviews, a food frequency questionnaire was used which ascertained the frequency of consumption of coffee, tea, and alcoholic beverages, as well as soft drinks that might contain caffeine. Serum uric acid was measured also.

Results

The survey used data from over 14,000 people aged over 20 years of age. Those with gout, or taking allopurinol or uricosuric agents were excluded.

Coffee, tea, and caffeine

Using a quintile of consumption approach, uric acid levels were identical across quintiles of intake of total caffeine and tea. For coffee (including decaffeinated), drinking more than four cups of coffee a day significantly lowered serum uric acid levels, by about 8% at maximum (Figure 1). The reduction of uric acid by coffee remained after adjusting for a whole range of variables and dietary factors.

Alcohol

Using the quintile of consumption approach drinking wine did not affect serum uric acid levels at any level of consumption up to one serving per day or more. The consumption

Figure 1: Reduction in mean serum uric acid levels according to quintiles of daily intake of coffee
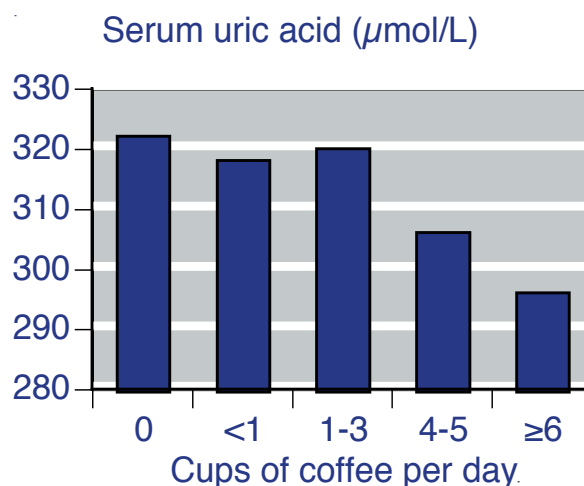
Figure 2: Effect of different daily consumption (quintiles) of different alcoholic beverages on mean serum uric acid levels
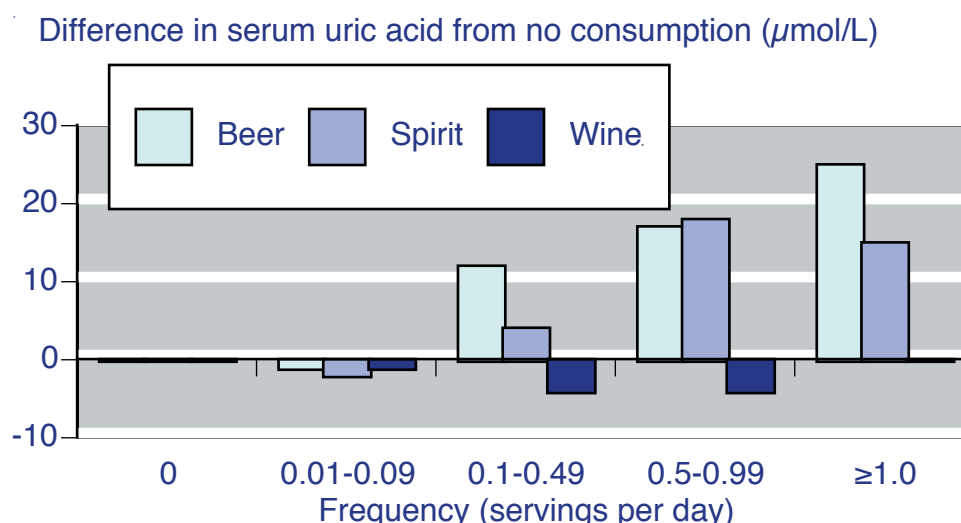
of spirits, and especially beer, did increase serum uric acid levels (Figure 2), even after adjusting for a whole range of factors. Beer and spirits drunk daily increased serum uric acid by about 10%; wine did not. The results were similar in men and women, and at lower and higher levels of BMI.

Comment

This constitutes useful additional knowledge about what gout suffers might do to avoid increasing their serum uric acid, and perhaps precipitating an attack, or making the pain worse. Drinking beer and spirits are out, but tea and wine have no effect, while coffee actually seems to reduce uric acid levels. We have had some straws in the wind about coffee before, but this adds weight.

More weight comes from a large study of coffee consumption and incident gout in men [3], following 46,000 men with no history of gout at baseline for 12 years. There were 750 cases of incident gout, and the risk was lower with higher coffee consumption, before and after adjustment for a whole host of different possible confounding factors (Figure 3). So increased coffee drinking is linked with both reduced serum uric acid levels and reduced incidence of clinical gout.

We also have information about what we eat and the risk of incident gout [4]. This has been examined in detail on the Bandolier Internet site, but the main results are worth reiterating. Increased consumption of meat was associated with increased risk of gout, but only with beef, pork, and lamb. There was less association with seafood, and none with purine rich vegetables. Increased consumption of dairy food reduced the risk of gout. We find the same now for uric acid [5] where high meat and to a small extent seafood consumption is associated with higher uric acid levels, but dairy food with lower uric acid levels. Much food for thought for those with gout and for healthy eating.

References:

1   HK Choi, G Curhan. Coffee, tea, and caffeine consumption and serum uric acid level: third National Health and Nutrition Examination Survey. Arthritis & Rheumatism 2007 57: 816-821.

Figure 3: Relative risk of incident gout in 12-year follow up of 46,000 men, according to quintiles of daily coffee consumption
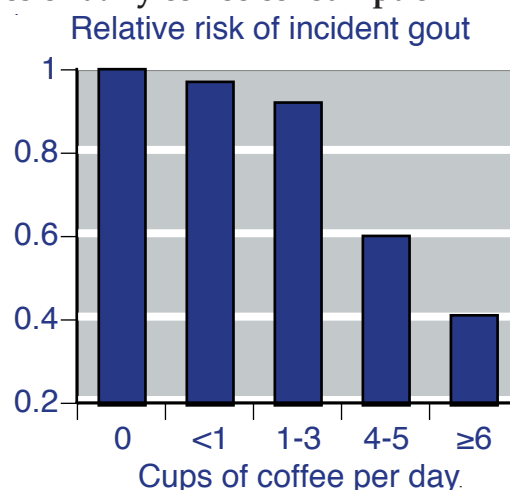
2   HK Choi, G Curhan. Beer, liquor, and wine consumption and serum uric acid level: third National Health and Nutrition Examination Survey. Arthritis & Rheumatism 2004 51: 1023-1029.

3   HK Choi et al. Coffee consumption and risk of incident gout in men. Arthritis & Rheumatism 2007 56: 2049-2055.

4   HK Choi et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. NEJM 2004 350:1093-1103.

5   HK Choi et al. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid. Arthritis & Rheumatism 2005 52: 283-289.